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(54) **Process for preparing sildenafil**

Verfahren zur Herstellung Sildenafil

Procédé pour la préparation de sildenafil

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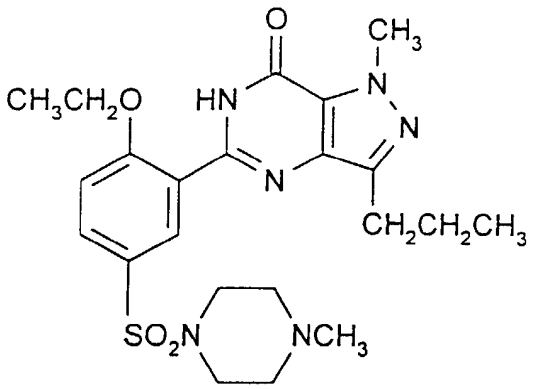
(56) References cited:
EP-A- 0 463 756 **EP-A- 0 526 004**
WO-A-94/28902

- **J.MED.CHEM, vol. 30, no. 1, 1987, pages 91-96, XP002040681 HAMILTON ET AL: "Synthesis and Structure-Activity Relationships of Pyrazolo[4,3-d "pyrimidin-7-ones as Adenosine Receptor Antagonists"**

EP 0 812 845 B1

Description

[0001] The invention relates to a process for the preparation of the compound of formula (I):

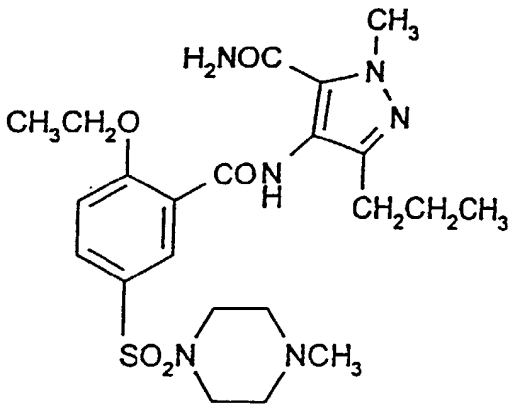


(I)

known as 5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo [4,3-d]pyrimidin-7-one or sildenafil, and also to intermediates used therein. Sildenafil, which was originally disclosed in EP-A-0463756, has been found to be particularly useful in the treatment of, inter alia, male erectile dysfunction: see WO-A-94/28902.

[0002] More specifically, the invention concerns a process for the preparation of sildenafil which is more efficient than that disclosed in EP-A-0463756 and which, surprisingly, can provide directly sildenafil of clinical quality standard, thus obviating the need for subsequent purification steps. In this context, sildenafil of clinical quality standard means material of sufficient purity for administration to humans.

[0003] The key step in the over-all process involves the ring-closure of the immediate precursor to sildenafil, i.e. the bis-amide of formula (II):



(II).

[0004] Thus the invention provides a process for the preparation of a compound of formula (I) which comprises cyclisation of a compound of formula (II).

[0005] An analogous cyclisation, which involves the use of polyphosphoric acid at 140°C, is disclosed in J. Med. Chem., 1987, 30, 91.

[0006] In a preferred embodiment, the cyclisation is carried out in the presence of a base, preferably in a solvent, optionally in the presence of hydrogen peroxide or a peroxide salt, and is followed, where necessary, by neutralisation of the reaction mixture.

[0007] A suitable base may be selected from the group consisting of a metal salt of any of the following: a C_1-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a (C_3-C_8 cycloalkyl)C_1-C_6 alkanol, ammonia, a C_1-C_{12} alkylamine, a di(C_1-C_{12} alkyl) amine, a C_3-C_8 cycloalkylamine, a N-(C_3-C_8 cycloalkyl)-N-(C_1-C_{12} alkyl)amine, a di(C_3-C_8 cycloalkyl)amine, a (C_3-C_8 cycloalkyl)C_1-C_6 alkylamine, a N-(C_3-C_8 cycloalkyl)C_1-C_6 alkyl-N-(C_1-C_{12} alkyl)amine, a N-(C_3-C_8 cycloalkyl)C_1-C_6

alkyl-N-(C_3-C_8 cycloalkyl)amine, a di[(C_3-C_8 cycloalkyl)C_1-C_6 alkyl]amine and a heterocyclic amine selected from the group consisting of imidazole, triazole, pyrrolidine, piperidine, heptamethyleneimine, morpholine, thiomorpholine and a 1-(C_1-C_4 alkyl)piperazine; a metal hydride, a metal hydroxide and a metal oxide; wherein the metal wherever referred to previously is selected from the group consisting of lithium, sodium, potassium, rubidium, cesium, beryllium, magnesium, calcium, strontium and barium.

[0008] Preferably the base is selected from the group consisting of an alkali or alkaline earth metal salt of a C_1-C_{12} alkanol, a C_3-C_{12} cycloalkanol and a (C_3-C_8 cycloalkyl) C_1-C_6 alkanol; an alkali metal salt of ammonia, a N-(secondary or tertiary C_3-C_6 alkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a C_3-C_8 cycloalkylamine, a N-(C_3-C_8 cycloalkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a di(C_3-C_8 cycloalkyl)amine and 1-methylpiperazine; and an alkali or alkaline earth metal hydride, hydroxide and oxide.

[0009] A suitable solvent may be selected from the group consisting of a C_1-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a (C_3-C_8 cycloalkyl)C_1-C_6 alkanol, a C_3-C_9 alkanone, a C_4-C_{10} cycloalkanone, a C_5-C_{12} alkyl ether, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, benzene, toluene, xylene, chlorobenzene, dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, dimethylacetamide, N-methylpyrrolidin-2-one, pyrrolidin-2-one, pyridine and water, and mixtures thereof.

[0010] Preferably the solvent is selected from the group consisting of ethanol, 2-propanol, a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a tertiary C_4-C_{12} cycloalkanol, a secondary or tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine and water, and mixtures thereof.

[0011] Further preferred features are that the quantity of base employed is from 1.0 to 5.0 molecular equivalents and that the reaction is carried out at from 50 to 170°C for from 3 to 170 hours.

[0012] In a more preferred process the base is selected from the group consisting of the lithium, sodium and potassium salts of a C_1-C_{12} alkanol, a C_4-C_{12} cycloalkanol, ammonia, cyclohexylamine and 1-methylpiperazine; the hydride salts of lithium, sodium and potassium; and barium oxide; the solvent is selected from the group consisting of ethanol, a tertiary C_4-C_{10} alcohol, a tertiary C_6-C_8 cycloalkanol, tetrahydrofuran, 1,4-dioxan and acetonitrile, the reaction is carried out at from 60 to 105°C and the quantity of base employed is from 1.1 to 2.0 molecular equivalents.

[0013] Even more preferred is a process wherein the base is selected from the group consisting of the C_1-C_{12} alkoxide and hydride salts of lithium, sodium and potassium, sodamide, sodium cyclohexylamide and cesium carbonate; the solvent is selected from the group consisting of ethanol, t-butanol, t-amyl alcohol, 1-methylcyclohexanol, tetrahydrofuran and 1,4-dioxan; and the reaction is conducted for from 3 to 60 hours.

[0014] A particularly preferred process is that wherein the base is selected from the group consisting of sodium ethoxide, sodium t-butoxide, potassium t-butoxide and sodium hydride; and the solvent is selected from the group consisting of ethanol, t-butanol, t-amyl alcohol and tetrahydrofuran.

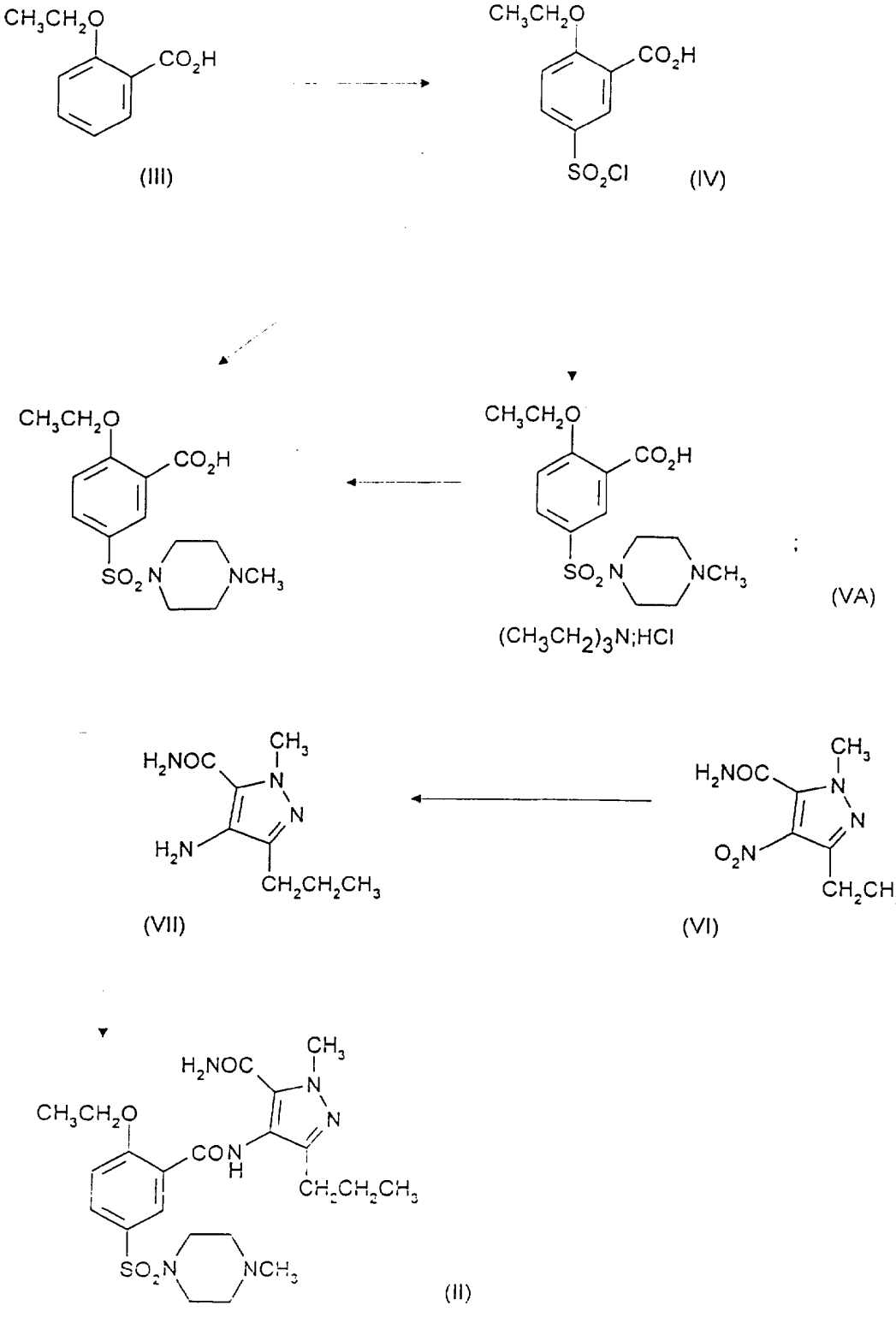
[0015] In the above definitions, unless otherwise stated, an alkyl chain or cycloalkyl ring may branched or unbranched.

[0016] The compound of formula (I) may be isolated and purified by conventional techniques. For example, when (I) is produced in the form of a salt, by neutralisation of the optionally prediluted reaction mixture, followed by collection of the product by filtration/extraction and optional crystallisation thereof.

[0017] Alternatively, the compound of formula (I) may be conveniently isolated and/or purified by standard chromatographic procedures.

[0018] The compound of formula (II) required for the preparation of the compound of formula (I) may be obtained by the route depicted in the following reaction scheme using conventional procedures.

SCHEME



[0019] Thus the compound of formula (IV) may be prepared by chlorosulphonylation of 2-ethoxybenzoic acid, i.e.

the compound of formula (III). Typically, (III) is added to an ice-cooled mixture of about 1 mol. equiv. of thionyl chloride and about 4 mol. equivs. of chlorosulphonic acid, whilst maintaining the reaction temperature below 25°C; the reaction is then allowed to continue at room temperature until complete.

[0020] Conversion of (IV) to the compound of formula (V) is achieved by N-sulphonylation of 1-methylpiperazine and may be conducted in a one-step or two-step procedure. In a one-step procedure, about 2.3 mol. equivs. of 1-methylpiperazine are added to an aqueous suspension of (IV) at about 10°C, whilst maintaining the reaction temperature below 20°C; the temperature of the resulting reaction mixture is then held at about 10°C. Alternatively, the quantity of 1-methylpiperazine can be reduced to about 1.1 mol. equiv. by employing about 1 mol. equiv. of sodium hydroxide as auxiliary base. In a two-step procedure, a solution of (IV) in a suitable solvent, e.g. acetone, is added to a mixture of about a 10% excess of 1 -methylpiperazine and about a 10% excess of a suitable acid acceptor, e.g. a tertiary base such as triethylamine, whilst maintaining the reaction temperature below 20°C. When triethylamine is employed as auxiliary base, an intermediate hydrochloride-triethylamine double salt of (V), identified as the compound of formula (VA), is isolated. This salt may be transformed to (V) by treatment with water.

[0021] A convenient alternative route to (V) is to employ a C_1-C_4 alkyl 2-ethoxybenzoate (obtained by conventional esterification of (III)) as the chlorosulphonylation substrate, followed by treatment of the resulting sulphonyl chloride with 1-methylpiperazine as described above, then subsequent standard hydrolysis of the ester group. Other synthetic options for obtaining (V) from salicylic acid and its derivatives will be apparent to the person skilled in the art.

[0022] Coupling of (V) with the compound of formula (VII) may be achieved by any of the plethora of amide bond-forming reactions well known to those skilled in the art. For example, the carboxylic acid function of (V) is first of all activated using about a 5% excess of a reagent such as N,N'- carbonyldiimidazole in a suitable solvent, e.g. ethyl acetate, at from about room temperature to about 80°C, followed by reaction of the intermediate imidazolide with (VII) at from about 20 to about 60°C.

[0023] The aminopyrazole (VII) is obtainable by conventional reduction of the corresponding nitropyrazole (VI), e.g. using palladium-catalysed hydrogenation in a suitable solvent such as ethyl acetate. The resulting solution of (VII) may be used directly, after filtration, in the coupling reaction with (V).

[0024] The cyclisation reaction of (II) to provide the compound of formula (I) has been achieved in yields of up to 95%. Thus the over-all yield of (I) based on the benzoic acid derivative (III) as starting material, depending on whether the one-step or two-step sulphonylation procedure is used, can be as high as 51.7% or 47.8% respectively. This compares very favourably with the process disclosed in EP-A-0463756 in which the over-all yield of (I) from 2-ethoxybenzoyl chloride (and thus from (III) also, assuming that the acid chloride derivative can be generated quantitatively therefrom) is 27.6%. In an alternative comparison, the over-all yield of (I) based on the nitropyrazole (VI) can be as high as 85.2% in the presently disclosed process whilst, in the process disclosed in EP-A-0463756, the over-all yield of (I) from (VI) is 23.1%.

[0025] Clearly then, the alternative process to (I) disclosed hereinbefore can be considerably more efficient and advantageous than that previously disclosed, and the intermediates of formulae (II), (V) and (VA) also form part of the invention.

[0026] The syntheses of the compound of formula (I) and the intermediates thereto are described in the following Examples and Preparations. In cases where the compound of formula (I) was not isolated and (if necessary) purified, the yields thereof were determined, and reaction mixtures analysed, by quantitative thin layer chromatography (TLC), using Merck silica gel 60 plates and toluene:methylated spirit:0880 aqueous ammonia mixtures as solvent systems, and/or high performance liquid chromatography (HPLC), using Gilson equipment with a 15 cm reverse phase C18 column and triethylamine:phosphoric acid buffer in aqueous acetonitrile:methanol mixtures as mobile phases.

[0027] ^{1}H Nuclear magnetic resonance (NMR) spectra were recorded using a Varian Unity 300 spectrometer and were in all cases consistent with the proposed structures. Characteristic chemical shifts (δ) are given in parts-per-million downfield from tetramethylsilane using conventional abbreviations for designation of significant peaks: e.g. s, singlet; d, doublet; t, triplet; q, quartet; h, hextet; m, multiplet; br, broad.

[0028] Room temperature means 20-25°C.

TITLE COMPOUND

5-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyllphenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d] pyrimidin-7-one

EXAMPLE 1

[0029] Potassium t-butoxide (3.37 g, 0.030 mol) was added to a stirred suspension of the title compound of Preparation 4 (12.32 g, 0.025 mol) in t-butanol (61 ml) and the resulting mixture heated under reflux for 8 hours, then allowed to cool to room temperature. Water (62.5 ml) was added and then the resulting solution filtered into a speck-free flask

and treated dropwise with a speck-free solution of concentrated hydrochloric acid (2.3 ml) in water (62.5 ml). The precipitated product was granulated at pH = 7 and 10°C for 1 hour, collected by filtration, washed with water and dried under vacuum to give the title compound (10.70 g, 90.2%) m.p. 189-190°C. Found: C,55.55; H,6.34; N,17.69. $C_{22}H_{30}N_6O_4S$ requires C,55.68; H,6.37; N,17.71%. δ (CD_3SOCD_3):0.94(3H,t), 1.32(3H,t), 1.73(2H,h), 2.15(3H,s), 2.35 (4H,br s), 2.76(2H,t), 2.88(4H,br s), 4.14(3H,s), 4.18(2H,q), 7.36(1H,d), 7.80(2H,m), 12.16(1 H,br s).

[0030] Analysis of the product by HPLC and quantitativeTLC indicated that clinical quality material had been obtained directly from the reaction.

[0031] The yield of clinical quality material can be increased to 95% by conducting the cyclisation under more concentrated conditions.

EXAMPLES 2-5

[0032] Clinical quality material was obtained by variation of the solvent, using procedures similar to that described in Example 1, as summarised in Table 1. As for Example 1, the reactions were carried out at reflux temperature, except in the cases of Examples 2 and 5 where a temperature of 100°C was employed.

TABLE 1

EXAMPLE	SOLVENT	REACTION TIME (HOURS)	% YIELD
2	t-amyl alcohol	5	78
3	ethanol	9.5	83
4	tetrahydrofuran	32	81
5	1-methylcyclohexanol	4	65

EXAMPLES 6-9

[0033] Clinical quality material was obtained by variation of the solvent and the base, using procedures similar to that described in Example 1, as summarised in Table 2. The reactions were carried out at reflux temperature, except in the case of Example 9 where a temperature of 100°C was employed.

TABLE 2

EXAMPLE	BASE	SOLVENT	REACTION TIME (HOURS)	% YIELD
6	sodium ethoxide	t-butanol	10	86
7	sodium ethoxide	ethanol	7	82.5
8	sodium hydride	tetrahydrofuran	48	84
9	cesium carbonate	t-amyl alcohol	17	71

EXAMPLE 10

[0034] Clinical quality material (88%) was obtained by variation of the cation, using a procedure similar to that described in Example 1, when sodium t-butoxide was used as base and the reaction was conducted for 24 hours.

EXAMPLE 11

[0035] Clinical quality material (71%) was obtained by variation of the molar ratio of base, using a procedure similar to that described in Example 1, when potassium t-butoxide (5.0 mol.equiv.) was used and the reaction was conducted at reflux temperature for 18 hours.

EXAMPLE 12

[0036] Further variation of the reaction conditions of Example 1, using 1.6 mol. equiv. of potassium t-butoxide (4.49 g, 0.040 mol) at 60°C for 55 hours, provided the title compound (87%) of purity >99% by HPLC and TLC analyses.

EXAMPLE 13

[0037] Title compound (87%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when 1,4-dioxan was used as solvent and the reaction was conducted at 100°C for 4 hours.

EXAMPLE 14

[0038] Title compound (85%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when 1,2-dimethoxyethane was used as solvent and the reaction was conducted for 30 hours.

EXAMPLE 15

[0039] Title compound (83%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when 3,7-dimethyloctan-3-ol was used as solvent and the reaction was conducted at 100°C for 16 hours.

EXAMPLE 16

[0040] Title compound (74%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when sodium n-decoxide was used as base, 1,4-dioxan was used as solvent and the reaction was conducted at 100°C for 20 hours.

EXAMPLE 17

[0041] Title compound (85%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when sodamide was used as base, 1,4-dioxan was used as solvent and the reaction was conducted at 100°C for 18 hours.

EXAMPLE 18

[0042] Title compound (91%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when sodium cyclohexylamide was used as base, 1,4-dioxan was used as solvent and the reaction was conducted at 100°C for 6.5 hours.

EXAMPLE 19

[0043] Title compound (84%) of purity >99% by HPLC and TLC analyses was obtained, using a procedure similar to that described in Example 1, when sodium 4-methylpiperazide was used as base, 1,4-dioxan was used as solvent and the reaction was conducted at 100°C for 8 hours.

EXAMPLES 20-21

[0044] Under reaction conditions similar to those described in Example 1, the use of sodium methoxide in methanol for 32 hours furnished a four-component mixture from which the title compound was isolated in a chromatographed yield of 34.5%, whilst the use of potassium t-butoxide in methanol for 40 hours afforded a product mixture which, by TLC and NMR spectroscopic analyses, contained an estimated yield of 69% of the title compound.

EXAMPLE 22

[0045] Under reaction conditions similar to those described in Example 1, the use of barium ethoxide (as a 10% w/v solution in ethanol) in t-amyl alcohol at 100°C for 20 hours provided a crude product (76.5% wt. yield) which, by TLC and HPLC analyses, contained an estimated yield of 75.5% of the title compound.

EXAMPLE 23

[0046] Under reaction conditions similar to those described in Example 1, the use of a total of 3.6 mol. equiv. (1.2

mol. equiv. added in three stages) of lithium diisopropylamide (as a 1.5M solution of the mono(tetrahydrofuran) complex in cyclohexane) in anhydrous 1,4-dioxan, initially at 0°C for 15 minutes, then at room temperature for 1 hour and subsequently at 100°C for a total of 140 hours, furnished a crude product (60.5% wt. yield) which, by TLC and HPLC analyses, contained an estimated yield of 55.5% of the title compound.

EXAMPLE 24

[0047] 85% Potassium hydroxide pellets (3.96 g, 0.06 mol) were added to a stirred suspension of the title compound of Preparation 4 (9.85 g, 0.02 mol) in ethanol (30 ml), followed by the addition of water (30 ml) which produced a clear solution. The reaction mixture was heated under reflux for 5 hours and then the bulk of the ethanol removed by evaporation under reduced pressure. The resulting mixture was diluted with water (60 ml), its pH adjusted to 7 using dilute sulphuric acid and the precipitated product granulated for 30 minutes. The solid was collected by filtration, washed with water and dried under vacuum to provide a product (7.96 g), 96.4% of which was shown, by HPLC analysis, to be the title compound.

EXAMPLES 25-27

[0048] Under reaction conditions similar to those described in Example 1, the use of barium oxide in acetonitrile at reflux temperature for 52 hours gave the title compound (89%) of purity >99% by HPLC and TLC analyses.

[0049] Repetition using dimethylformamide as solvent at 100°C for 31 hours provided a crude product (75.5% wt. yield) which, by TLC and HPLC analyses, contained an estimated yield of 54% of the title compound.

[0050] Further repetition using pyridine as solvent at 100°C for 16 hours fumished a crude product which, by TLC and HPLC analyses, contained a maximum (due to barium salt contamination) estimated yield of 90% of the title compound.

PREPARATION 1

5-Chlorosulphonyl-2-ethoxybenzoic acid

[0051] Molten 2-ethoxybenzoic acid (25.0 g, 0.150 mol) was added to a stirred, ice-cooled mixture of thionyl chloride (11 ml, 0.151 mol) and chlorosulphonic acid (41.3 ml, 0.621 mol), whilst maintaining the temperature of the reaction mixture below 25°C. The resulting mixture was stirred at room temperature for 18 hours and then poured into a stirred mixture of ice (270 g) and water (60 ml) to give an off-white precipitate. Stirring was continued for 1 hour, then the product was collected by filtration, washed with water and dried under vacuum to provide the title compound (36.08 g). A reference sample, m.p. 115-116°C, was obtained by crystallisation from hexane:toluene. Found: C,41.02; H,3.27. $C_9H_9ClO_5S$ requires C,40.84; H,3.43%. δ ($CDCl_3$): 1.64(3H,t), 4.45(2H,q), 7.26(1H,d), 8.20(1H,dd), 8.80(1 H,d).

PREPARATION 2

2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)benzoic acid

(a): one-step procedure

[0052] 1-Methylpiperazine (33.6 ml, 0.303 mol) was added to a stirred suspension of the title compound of Preparation 1 (34.4 g, 0.130 mol) in water (124 ml) at about 10°C, whilst maintaining the temperature of the reaction mixture below 20°C. The resulting solution was cooled to about 10°C and, after 5 minutes, crystallisation of a solid commenced. After a further 2 hours, the solid was collected by filtration, washed with ice-water and dried under vacuum to furnish the crude product (36.7 g). A sample (15.0 g) was purified by stirring it in refluxing acetone for 1 hour; the resulting suspension was allowed to cool to room temperature and the crystalline solid collected by filtration and dried under vacuum to afford the title compound (11.7 g), m.p. 198-199°C, whose ^1H nmr spectrum is identical with that obtained for the product of procedure (b) below.

(b): two-step procedure

[0053] A solution of the title compound of Preparation 1 (50.0 g, 0.189 mol) in acetone (150 ml) was added dropwise to a stirred mixture of 1-methylpiperazine (20.81 g, 0.208 mol) and triethylamine (28.9 ml, 0.207 mol), whilst maintaining the temperature of the reaction mixture below 20°C. A white crystalline solid formed during the addition and stirring was continued for a further 1.5 hours. Filtration, followed by washing with acetone and drying under vacuum of the

product, provided the hydrochloride-triethylamine double salt of the title compound (78.97 g), m.p. 166-169°C. Found: C,51.33; H,8.14; N,9.06; C1,8.02. $C_{14}H_{20}N_2O_5S$; $C_6H_{15}N$; HCl requires C,51.55; H,7.79; N,9.02; Cl, 7.61%. δ (CD_3SOCD_3): 1.17(9H,t), 1.32(3H,t), 2.15(3H,s), 2.47(6H,br s), 2.86(2H, br s), 3.02(6H,q), 4.18(2H,q), 7.32(1H,d), 7.78(1H,dd), 7.85(1H,d).

[0054] The double salt (30.0 g) was stirred in water (120 ml) to produce an almost clear solution, from which crystallisation of a solid rapidly occurred. After 2 hours, the solid was collected by filtration, washed with water and dried under vacuum to give the title compound (14.61 g) as a white solid. A reference sample, m.p. 201°C, was obtained by recrystallisation from aqueous ethanol. Found: C,51.09; H,6.16; N,8.43. $C_{14}H_{20}N_2O_5S$ requires C,51.21; H,6.14; N, 8.53%. δ (CD_3SOCD_3): 1.31(3H,t), 2.12(3H,s), 2.34(4H,br s), 2.84(4H, br s), 4.20(2H,q), 7.32(1H,d), 7.80(1H,dd), 7.86 (1H,d).

PREPARATION 3

4-Amino-1-methyl-3-n-propylpyrazole-5-carboxamide

[0055] A stirred suspension of 1-methyl-4-nitro-3-n-propylpyrazole-5-carboxamide (EP-A-0463756; 237.7g, 1.12 mol) and 5% palladium on charcoal (47.5 g) in ethyl acetate (2.02 l) was hydrogenated at 344.7 kPa (50 psi) and 50°C for 4 hours, when the uptake of hydrogen was complete. The cool reaction mixture was filtered, then the filter pad washed with ethyl acetate, the combined filtrate and washings thus fumishing an ethyl acetate solution of the title compound (EP-A-0463756) which was of sufficient purity to use directly in the next stage of the reaction sequence (see Preparation 4).

PREPARATION 4

4-[2-Ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)benzamido]-1-methyl-3-n-propylpyrazole-5-carboxamide

[0056] N,N'-Carbonyldiimidazole (210.8 g, 1.30 mol) was washed into a stirred suspension of the title compound of Preparation 2 (408.6 g, 1.24 mol) in ethyl acetate (1.50 l) using ethyl acetate (1.36 l) and the resulting mixture heated at 55°C for 0.5 hour and then under reflux for a further 2 hours before being allowed to cool to room temperature. An ethyl acetate solution of the title compound of Preparation 3 (2.185 Kg of solution containing 204 g, 1.12 mol of amine) was added and the reaction mixture stirred at room temperature for 72 hours to afford a crystalline solid which was collected by filtration and dried under vacuum. The title compound (425 g), m.p. 204-206°C, thus obtained was combined with a further crop (70 g) which was recovered by concentration of the mother liquor. A reference sample, m.p. 206-208°C, was obtained by recrystallisation from aqueous methanol. Found: C,53.65; H,6.54; N,17.07. $C_{22}H_{32}N_6O_5S$ requires C,53.64; H,6.55; N,17.06%. δ ($CDCl_3$): 0.96(3H,t), 1.58(3H,t), 1.66(2H,m), 2.27(3H,s), 2.45(4H,m), 2.52(2H, t), 3.05(4H,br s), 4.05(3H,s), 4.40(2H,q), 5.61(1H, br s), 7.61(1H,d), 7.65(1H, br s), 7.90(1H,dd), 8.62(1H,d), 9.25(1H, br s).

PREPARATION 5

Methyl 2-ethoxybenzoate

[0057] Concentrated sulphuric acid (0.5 ml) was added to a solution of 2-ethoxybenzoic acid (50 g, 0.301 mol) in methanol (500 ml) and the resulting mixture heated under reflux for 70 hours, then evaporated under reduced pressure to give an oil which was dissolved in dichloromethane (300 ml). This solution was washed successively with water (150 ml), aqueous sodium bicarbonate solution (150 ml) and water (150 ml), then evaporated under reduced pressure to give the title compound (49.7 g) as an oil. δ ($CDCl_3$): 1.44 (3H,t), 3.90 (3H,s), 4.12 (2H,q), 6.95 (2H,m), 7.44 (1H,t), 7.78 (1H,d).

PREPARATION 6

Methyl 5-chlorosulphonyl-2-ethoxybenzoate

[0058] The title compound of Preparation 5 (36.04 g, 0.20 mol) was added dropwise 5 over 10 minutes to stirred, ice-cooled chlorosulphonic acid (59.8 ml, 0.90 mol), whilst maintaining the temperature of the reaction mixture below 22°C. The reaction mixture was stirred at room temperature for 18 hours, then thionyl chloride (14.6 ml, 0.20 mol) added and the resulting solution stirred at room temperature for 6 hours, then poured into a stirred mixture of ice (530 g) and water (120 ml). The quenched mixture was extracted with dichloromethane (2 x 200 ml) and the combined

extracts evaporated under reduced pressure to give the crude title compound (44.87 g) as a white solid. A reference sample, m.p. 99-100°C, was obtained by crystallisation from toluene. δ ($CDCl_3$): 1.52 (3H,t), 3.93 (3H,s), 4.25 (2H,q), 4.25 (2H,q), 7.12 (1H,d), 8.12 (1H,dd), 8.46 (1H,d).

PREPARATION 7

Methyl 2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)benzoate

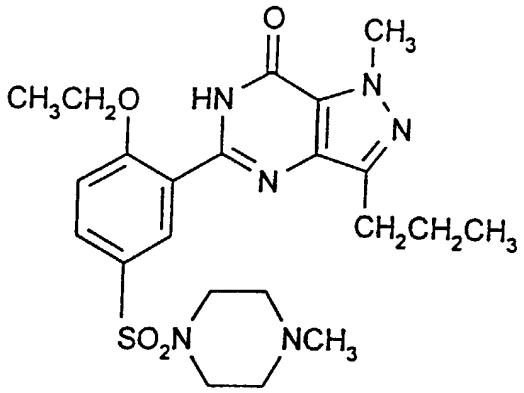
[0059] A solution of the crude title compound of Preparation 6 (27.87 g) in acetone (140 ml) was added dropwise over 10 minutes to a stirred, ice-cooled solution of 1-methylpiperazine (11.02 g, 0.11 mol) and triethylamine (15.3 ml, 0.11 mol) in acetone (140 ml), whilst maintaining the temperature of the reaction mixture below 20°C. A white precipitate formed during the addition and stirring was continued for a further 4 hours. The resulting mixture was filtered, the filtrate evaporated under reduced pressure and the residue azeotroped with toluene to provide a pale brown gum (41.9 g). This crude product was granulated by stirring with water (100 ml) for 2 hours and the resulting material collected by filtration, washed with water (2 x 50 ml) and dried under vacuum at 50°C to furnish the title compound, m.p. 110-111°C. δ ($CDCl_3$): 1.48 (3H,t), 2.27 (3H,s), 2.47 (4H,t), 3.03 (4H,t), 3.90 (3H,s), 4.18 (2H,q), 7.04 (1H,d), 7.81 (1H,dd), 8.15 (1H,d).

[0060] The compound obtained as above was shown to be identical with that produced by conventional methyl esterification of the title compound of Preparation 2.

[0061] Furthermore, conventional base hydrolysis of the compound obtained as above afforded a product identical with that of Preparation 2.

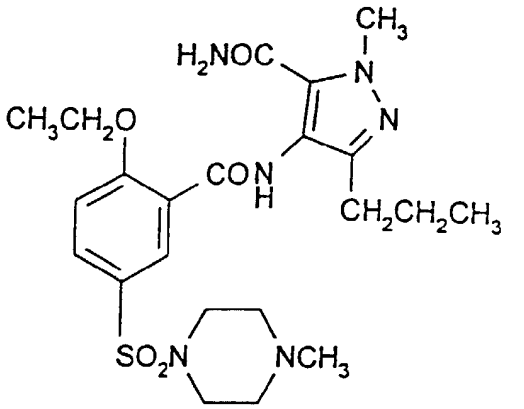
Claims

1. A process for the preparation of a compound of formula (I):



(I)

which comprises cyclisation of a compound of formula (II):



(II)

wherein the cyclisation is carried out in the presence of a base, preferably in a solvent, optionally in the presence of hydrogen peroxide or a peroxide salt, and is followed, where necessary, by neutralisation of the reaction mixture; and wherein the base is selected from the group consisting of a metal salt of any of the following: a C_1-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a (C_3-C_8 cycloalkyl)C_1-C_6 alkanol, ammonia, a C_1-C_{12} alkylamine, a di(C_1-C_{12} alkyl)amine, a C_3-C_8 cycloalkylamine, a N-(C_3-C_8 cycloalkyl)-N-(C_1-C_{12} alkyl)amine, a di(C_3-C_8 cycloalkyl)amine, a (C_3-C_8 cycloalkyl)C_1-C_6 alkylamine, a N-(C_3-C_8 cycloalkyl)C_1-C_6 alkyl-N-(C_1-C_{12} alkyl)amine, a N-(C_3-C_8 cycloalkyl)C_1-C_6 alkyl-N-(C_3-C_8 cycloalkyl)amine, a di[(C_3-C_8 cycloalkyl)C_1-C_6 alkyl]amine and a heterocyclic amine selected from the group consisting of imidazole, triazole, pyrrolidine, piperidine, heptamethyleneimine, morpholine, thiomorpholine and a 1-(C_1-C_4 alkyl)piperazine; a metal hydride, a metal hydroxide and a metal oxide; wherein the metal wherever referred to previously is selected from the group consisting of lithium, sodium, potassium, rubidium cesium, beryllium, magnesium, calcium, strontium and barium;
and the solvent is selected from the group consisting of a C_1-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a (C_3-C_8 cycloalkyl) C_1-C_6 alkanol, a C_3-C_9 alkanone, a C_4-C_{10} cycloalkanone, a C_5-C_{12} alkyl ether, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, benzene, toluene, xylene, chlorobenzene, dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, dimethylacetamide, N-methylpyrrolidin-2-one, pyrrolidin-2-one, pyridine and water, and mixtures thereof.

2. A process according to claim I wherein the base is selected from the group consisting of an alkali or alkaline earth metal salt of a C_1-C_{12} alkanol, a C_3-C_{12} cycloalkanol and a (C_3-C_8 cycloalkyl)C_1-C_6 alkanol; an alkali metal salt of ammonia, a N-(secondary or tertiary C_3-C_6 alkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a C_3-C_8 cycloalkylamine, a N-(C_3-C_8 cycloalkyl)-N-(primary, secondary or tertiary C_3-C_6 alkyl)amine, a di(C_3-C_8 cycloalkyl) amine and 1-methylpiperazine; an alkali or alkaline earth metal hydride, hydroxide and oxide;
and the solvent is selected from the group consisting of ethanol, 2-propanol, a secondary or tertiary C_4-C_{12} alkanol, a C_3-C_{12} cycloalkanol, a tertiary C_4-C_{12} cycloalkanol, a secondary or tertiary (C_3-C_7 cycloalkyl)C_2-C_6 alkanol, a C_3-C_9 alkanone, 1,2-dimethoxyethane, 1,2-diethoxyethane, diglyme, tetrahydrofuran, 1,4-dioxan, toluene, xylene, chlorobenzene, 1,2-dichlorobenzene, acetonitrile, dimethyl sulphoxide, sulpholane, dimethylformamide, N-methylpyrrolidin-2-one, pyridine and water, and mixtures thereof.

3. A process according to either of claims 1 and 2 wherein the reaction is carried out at from 50 to 170°C for from 3 to 170 hours.

4. A process according to claim 3 wherein the quantity of base employed is from 1.0 to 5.0 molecular equivalents.

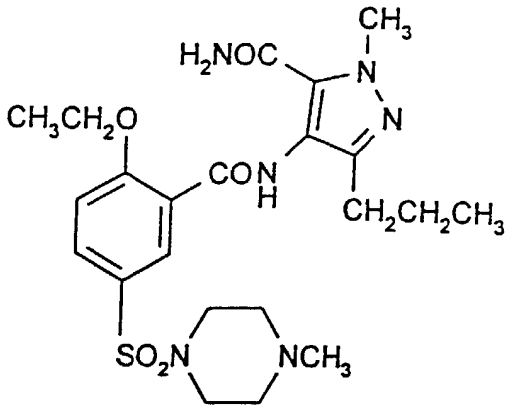
5. A process according to claim 4 wherein the base is selected from the group consisting of the lithium, sodium and potassium salts of a C_1-C_{12} alkanol, a C_4-C_{12} cycloalkanol, ammonia, cyclohexylamine and 1-methylpiperazine; the hydride salts of lithium, sodium and potassium; and barium oxide; the solvent is selected from the group consisting of ethanol, a tertiary C_4-C_{10} alcohol, a tertiary C_6-C_8 cycloalkanol, tetrahydrofuran, 1,4-dioxan and acetonitrile, the reaction is carried out at from 60 to 105°C and the quantity of base employed is from 1.1 to 2.0 molecular equivalents.

6. A process according to claim 5 wherein the base is selected from the group consisting of the C_1-C_{12} alkoxide and

hydride salts of lithium, sodium and potassium, sodamide and sodium cyclohexylamide; the solvent is selected from the group consisting of ethanol, t-butanol, t-amyl alcohol, 1-methylcyclohexanol, tetrahydrofuran and 1,4-dioxan; and the reaction is conducted for from 3 to 60 hours.

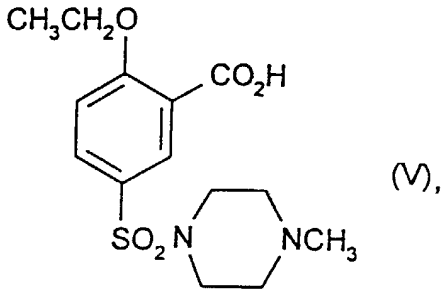
7. A process according to claim wherein the base is selected from the group consisting of sodium ethoxide, sodium t-butoxide, potassium t-butoxide and sodium hydride; and the solvent is selected from the group consisting of ethanol, t-butanol, t-amyl alcohol and tetrahydrofuran.

8. A compound of formula (II):



(II).

9. A compound of formula (V):

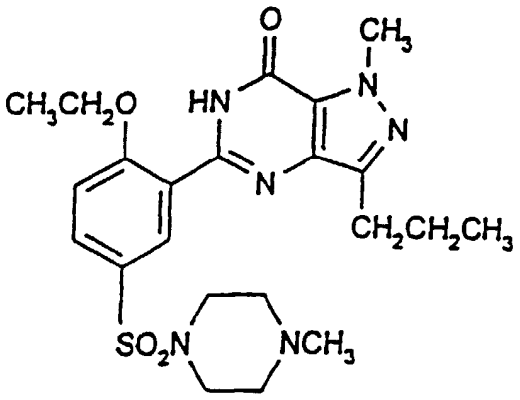


(V),

or the hydrochloride-triethylamine double salt thereof, or a C_1-C_4 alkyl ester thereof.

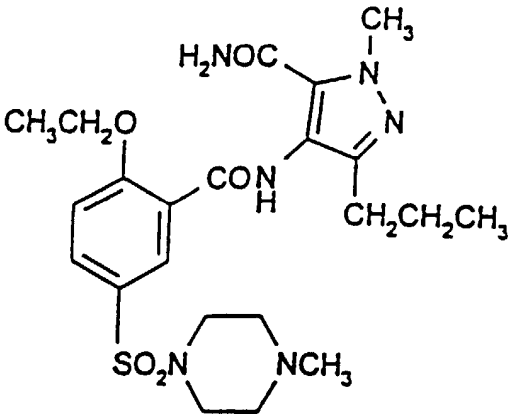
Patentansprüche

1. Verfahren zur Herstellung einer Verbindung der Formel (I):



(I)

das Cyclisierung einer Verbindung der Formel (II):



(II)

umfaßt, wobei die Cyclisierung in Gegenwart einer Base, vorzugsweise in einem Lösungsmittel, gegebenenfalls in Gegenwart von Wasserstoffperoxid oder einem Peroxidsalz ausgeführt wird, und, falls erforderlich, von der Neutralisation des Reaktionsgemisches gefolgt wird; und wobei die Base, ausgewählt ist aus der Gruppe, bestehend aus einem Metallsalz von einem der nachstehenden Stoffe: einem C_1-C_{12}-Alkanol, einem C_3-C_{12}-Cycloalkanol, einem (C_3-C_8-Cycloalkyl)C_1-C_6-alkanol, Ammoniak, einem C_1-C_{12}-Alkylamin, einem Di(C_1-C_{12}-alkyl) amin, einem C_3-C_8-Cycloalkylamin, einem N-(C_3-C_8-Cycloalkyl) -N- (C_1-C_{12}-alkyl) amin, einem Di(C_3-C_8-cycloalkyl)amin, einem (C_3-C_8-Cycloalkyl)C_1-C_6-alkylamin, einem N-(C_3-C_8-Cycloalkyl)C_1-C_6-alkyl-N-(C_1-C_{12}-alkyl) amin, einem N-(C_3-C_8-Cycloalkyl)C_1-C_6-alkyl-N-(C_3-C_8-cycloalkyl)amin, einem Di[(C_3-C_8-cycloalkyl)C_1-C_6-alkyl] amin und einem heterocyclischen Amin, ausgewählt aus der Gruppe, bestehend aus Imidazol, Triazol, Pyrrolidin, Piperidin, Heptamethylenimin, Morpholin, Thiomorpholin und einem 1-(C_1-C_4-Alkyl)piperazin; einem Metallhydrid, einem Metallhydroxid und einem Metalloxid; wobei das Metall, wenn immer vorstehend darauf Bezug genommen wird, ausgewählt ist aus der Gruppe, bestehend aus Lithium, Natrium, Kalium, Rubidium, Cäsium, Beryllium, Magnesium, Kalzium, Strontium und Barium;

und das Lösungsmittel ausgewählt ist aus der Gruppe, bestehend aus einem C_1-C_{12}-Alkanol, einem C_3-C_{12}-Cycloalkanol, einem (C_3-C_8-Cycloalkyl)C_1-C_6-alkanol, einem C_3-C_9-Alkanon, einem C_4-C_{10}-Cycloalkanon, einem C_5-C_{12}-Alkylether, 1,2-Dimethoxyethan, 1,2-Diethoxyethan, Diglym, Tetrahydrofuran, 1,4-Dioxan, Benzol, Toluol, Xylol, Chlorbenzol, Dichlorbenzol, Acetonitril, Dimethylsulfoxid, Sulfolan, Dimethylformamid, Dimethylacetamid, N-Methylpyrrolidin-2-on, Pyrrolidin-2-on, Pyridin und Wasser und Gemischen davon.

2. Verfahren nach Anspruch 1, wobei die Base ausgewählt ist aus der Gruppe, bestehend aus einem Alkali- oder Erdalkalimetallsalz von einem C_1-C_{12}-Alkanol, einem C_3-C_{12}-Cycloalkanol und einem (C_3-C_8-Cycloalkyl)C_1-C_6-alkanol; einem Alkalimetallsalz von Ammoniak, einem N-(sekundären oder tertiären C_3-C_6-Alkyl)-N-(primären, sekundären oder tertiären C_3-C_6-Alkyl)amin, einem C_3-C_8-Cycloalkylamin, einem N-(C_3-C_8-Cycloalkyl)-N-(primären, sekundären oder tertiären C_3-C_6-Alkyl)amin, einem Di(C_3-C_8-cycloalkyl)amin und 1-Methylpiperazin; einem Alkali- oder Erdalkalimetallhydrid, -hydroxid und -oxid;

und das Lösungsmittel ausgewählt ist aus der Gruppe, bestehend aus Ethanol, 2-Propanol, einem sekundären oder tertiären C_4-C_{12}-Alkanol, einem C_3-C_{12}-Cycloalkanol, einem tertiären C_4-C_{12}-Cycloalkanol, einem sekundären oder tertiären (C_3-C_7-Cycloalkyl)C_2-C_6-alkanol, einem C_3-C_9-Alkanon, 1,2-Dimethoxyethan, 1,2-Diethoxyethan, Diglym, Tetrahydrofuran, 1,4-Dioxan, Toluol, Xylol, Chlorbenzol, 1,2-Dichlorbenzol, Acetonitril, Dimethylsulfoxid, Sulfolan, Dimethylformamid, N-Methylpyrrolidin-2-on, Pyridin und Wasser und Gemischen davon.

3. Verfahren nach einem der Ansprüche 1 und 2, wobei die Umsetzung bei 50 bis 170°C für 3 bis 170 Stunden ausgeführt wird.

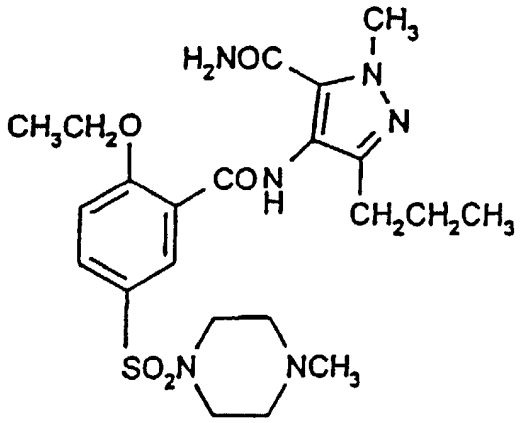
4. Verfahren nach Anspruch 3, wobei die Menge der angewendeten Base 1,0 bis 5,0 Moläquivalente ist.

5. Verfahren nach Anspruch 4, wobei die Base ausgewählt ist aus der Gruppe, bestehend aus Lithium-, Natrium- und Kaliumsalzen von einem C_1-C_{12}-Alkanol, einem C_4-C_{12}-Cycloalkanol, Ammoniak, Cyclohexylamin und 1-Methylpiperazin; den Hydridsalzen von Lithium, Natrium und Kalium; und Bariumoxid; das Lösungsmittel ausgewählt ist aus der Gruppe, bestehend aus Ethanol, einem tertiären C_4-C_{10}-Alkohol, einem tertiären C_6-C_8-Cycloalkanol, Tetrahydrofuran, 1,4-Dioxan und Acetonitril, wobei die Umsetzung bei 60 bis 105°C ausgeführt wird und die angewendete Basenmenge 1,1 bis 2,0 Moläquivalente ist.

6. Verfahren nach Anspruch 5, wobei die Base ausgewählt ist aus der Gruppe, bestehend aus den C_1-C_{12}-Alkoxid- und Hydridsalzen von Lithium, Natrium und Kalium, Natriumamid und Natriumcyclohexylamid; das Lösungsmittel ausgewählt ist aus der Gruppe, bestehend aus Ethanol, t-Butanol, t-Amylalkohol, 1-Methylcyclohexanol, Tetrahydrofuran und 1,4-Dioxan; und die Umsetzung 3 bis 60 Stunden durchgeführt wird.

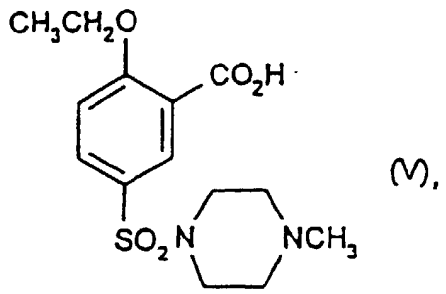
7. Verfahren nach Anspruch 6, wobei die Base ausgewählt ist aus der Gruppe, bestehend aus Natriumethoxid, Natrium-t-butoxid, Kalium-t-butoxid und Natriumhydrid; und das Lösungsmittel ausgewählt ist aus der Gruppe, bestehend aus Ethanol, t-Butanol, t-Amylalkohol und Tetrahydrofuran.

8. Verbindung der Formel (II):



(II).

9. Verbindung der Formel (V):

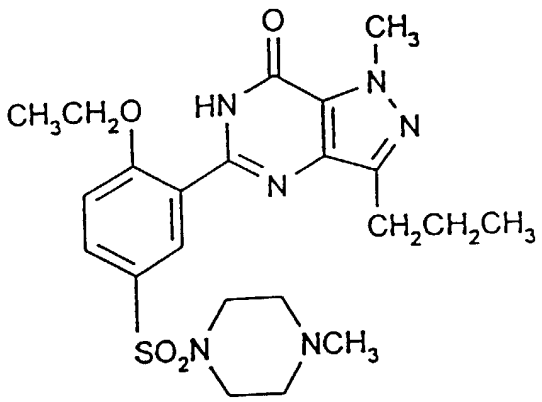


(V),

oder das Hydrochlorid-Triethylamin-Doppelsalz davon, oder ein C_1-C_4-Alkylester davon.

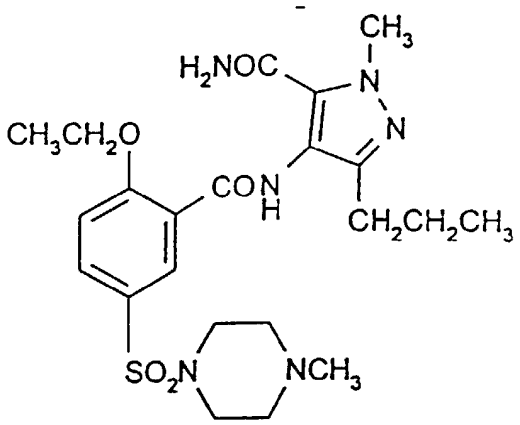
Revendications

1. Procédé pour la préparation d'un composé de formule (I) :



(I)

qui comprend la cyclisation d'un composé de formule (II) :



(II)

la cyclisation étant effectuée en présence d'une base, de préférence dans un solvant, facultativement en présence de peroxyde d'hydrogène ou d'un sel d'un peroxyde, et étant suivie, lorsque cela est nécessaire, par une neutralisation du mélange réactionnel ;

et la base étant choisie dans le groupe consistant en un sel métallique de n'importe lequel des composés

suivants : un alcanol en C_1 à C_{12} ; un cyclo-alcanol en C_3 à C_{12} ; un (cycloalkyle en C_3 à C_8)-(alcanol en C_1 à C_6), l'ammoniac, une alkylamine en C_1 à C_{12} ; une di-(alkyle en C_1 à C_{12})-amine, une cycloalkylamine en C_3 à C_8, une N-(cycloalkyle en C_3 à C_8)-N-(alkyle en C_1 à C_{12})-amine, une di-(cycloalkyle en C_3 à C_8)-amine, une (cycloalkyle en C_3 à C_8)-(alkyle en C_1 à C_6)-amine, une N-(cycloalkyle en C_3 à C_8)-(alkyle en C_1 à C_6)-N-(alkyle en C_1 à C_{12})-amine, une N-(cycloalkyle en C_3 à C_8)-(alkyle en C_1 à C_6)-N-(cycloalkyle en C_3 à C_8)-amine, une di-[(cycloalkyle en C_3 à C_8)-(alkyle en C_1 à C_6)]-amine et une amine hétérocyclique choisie dans le groupe consistant en imidazole, triazole, pyrrolidine, pipéridine, heptaméthylèneimine, morpholine, thiomorpholine et une 1-(alkyle en C_1 à C_4)-pipérazine ; un hydrure métallique ; un hydroxyde métallique et un oxyde métallique ; le métal, chaque fois qu'il est mentionné précédemment, étant choisi dans le groupe consistant en lithium, sodium, potassium, rubidium, césium, béryllium, magnésium, calcium, strontium et baryum ; et le solvant étant choisi dans le groupe consistant en un alcanol en C_1 à C_{12}, un cyclo-alcanol en C_3 à C_{12}, un (cycloalkyle en C_3 à C_8)-(alcanol en C_1 à C_6) ; une alcanone en C_3 à C_9, un cyclo-alcanone en C_4 à C_{10}, un éther d'alkyle en C_5 à C_{12}, le 1,2-diméthoxy-éthane, le 1,2-diéthoxy-éthane, le diglyme, le tétrahydrofuranne, le 1,4-dioxane, le benzène, le toluène, le xylène, le chlorobenzène, le dichlorobenzène, l'acétonitrile, le diméthylsulfoxyde, le sulfolane, le diméthylformamide, le diméthylacétamide, la N-méthylpyrrolidine-2-one, la pyrrolidine-2-one, la pyridine et l'eau, ainsi que leurs mélanges.

2. Procédé suivant la revendication 1, dans lequel la base est choisie dans le groupe consistant en un sel de métal alcalin ou de métal alcalino-terreux d'un alcanol en C_1 à C_{12}, d'un cycloalcanol en C_3 à C_{12} ou d'un (cycloalkyle en C_3 à C_8)-(alcanol en C_1 à C_8); un sel de métal alcalin de l'ammoniac, d'une N-(alkyle secondaire ou tertiaire en C_3 à C_6)-N-(alkyle primaire, secondaire ou tertiaire en C_3 à C_6)-amine, d'une cycloalkylamine en C_3 à C_8, d'une N-(cycloalkyle en C_3 à C_8)-N-(alkyle primaire, secondaire ou tertiaire en C_3 à C_6)-amine, d'une di-(cycloalkyle en C_3 à C_8)-amine et de la 1-méthylpipérazine ; un hydrure, hydroxyde ou oxyde de métal alcalin ou de métal alcalino-terreux ;
et le solvant est choisi dans le groupe consistant en éthanol, 2-propanol, un alcanol secondaire ou tertiaire en C_4 à C_{12}, un cycloalcanol en C_3 à C_{12}, un cycloalcanole tertiaire en C_4 à C_{12}, un (cycloalkyle en C_3 à C_7)-(alcanol en C_2 à C_6) secondaire ou tertiaire, une alcanone en C_3 à C_9, le 1,2-diméthoxy-éthane, le 1,2-diéthoxy-éthane, le diglyme, le tétrahydrofuranne, le 1,4-dioxane, le toluène, le xylène, le chlorobenzène, le 1,2-dichlorobenzène, l'acétonitrile, le diméthylsulfoxyde, le sulfolane, le diméthylformamide, la N-méthylpyrrolidine-2-one, la pyridine et l'eau, ainsi que leurs mélanges.

3. Procédé suivant l'une des revendications 1 et 2, dans lequel la réaction est conduite à une température comprise dans l'intervalle de 50 à 170°C pendant un temps de 3 à 170 heures.

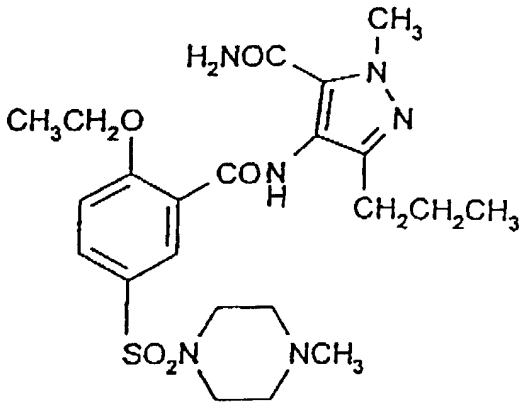
4. Procédé suivant la revendication 3, dans lequel la quantité de base utilisée est comprise dans l'intervalle de 1,0 à 5,0 équivalents molaires.

5. Procédé suivant la revendication 4, dans lequel la base est choisie dans le groupe consistant en les sels de lithium, de sodium et de potassium d'un alcanol en C_1 à C_{12}, d'un cycloalcanol en C_4 à C_{12}, de l'ammoniac, de la cyclohexylamine et de la 1-méthylpipérazine ; les hydrures de lithium, de sodium et de potassium ; et l'oxyde de baryum ; le solvant est choisi dans le groupe consistant en éthanol, un alcool tertiaire en C_4 à C_{10}, un cycloalcanol tertiaire en C_6 à C_8, le tétrahydrofuranne, le 1,4-dioxane et l'acétonitrile, la réaction est conduite à une température comprise dans l'intervalle de 60 à 105°C et la quantité de base utilisée est comprise dans l'intervalle de 1,1 à 2,0 équivalents molaires.

6. Procédé suivant la revendication 5, dans lequel la base est choisie dans le groupe consistant en des alcoolates en C_1 à C_{12} et hydrures de lithium, de sodium et de potassium, le sodamide et le cyclohexylamidure de sodium ; le solvant est choisi dans le groupe consistant en éthanol, tertiobutanol, alcool tertio-amylique, 1-méthylcyclohexanone, tétrahydrofuranne et 1,4-dioxane ; et la réaction est conduite pendant un temps de 3 à 60 heures.

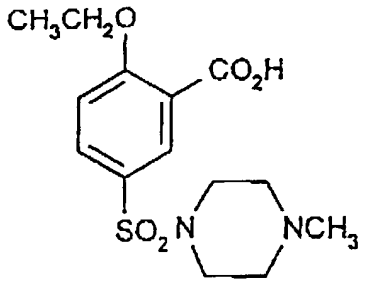
7. Procédé suivant la revendication 6, dans lequel la base est choisie dans le groupe consistant en éthylate de sodium, tertiobutylate de sodium, tertiobutylate de potassium et hydrure de sodium ; et le solvant est choisi dans le groupe consistant en éthanol, tertiobutanol, alcool tertio-amylique et tétrahydrofuranne.

8. Composé de formule (II) :



(II).

9. Composé de formule (V) :



(V),

ou son sel double consistant en chlorhydrate-sel de triéthylamine, ou un de ses esters d'alkyle en C_1 à C_4.